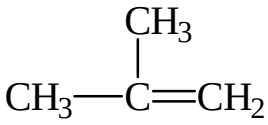
ABSTRACT



ISOBUTENE

CAS No. 115-11-7

Chemical Formula: C_4H_8 Molecular Weight: 56.10

Synonyms: Isobutylene, 2-methylpropene, liquified petroleum gas, γ-butylene

Isobutene is produced during the fractionation of refinery gases or through the catalytic cracking of methyl-*t*-butyl ether. Isobutene is primarily used to produce diisobutylene, trimers, butyl rubber, and other polymers. In addition, it is used in the production of isooctane, high-octane aviation gasoline, methyl-*t*-butyl ether, and copolymer resins with butadiene and acrylonitrile. Isobutene was selected for evaluation because of the potential for human exposure due to its large production volume and the lack of adequate data on its carcinogenic potential. The toxicity and carcinogenicity of isobutene were determined in male and female F344/N rats and B6C3F$_1$ mice exposed to isobutene (greater than 98% pure) by inhalation for 14 weeks or 2 years. The mutagenicity of isobutene was assessed in *Salmonella typhimurium,* and the frequency of micronuclei was determined in the peripheral blood of mice exposed by inhalation for 14 weeks.

14-WEEK STUDY IN RATS

Groups of 10 male and 10 female F344/N rats were exposed to isobutene at concentrations of 0, 500, 1,000, 2,000, 4,000, or 8,000 ppm 6 hours per day, 5 days per week, for 14 weeks. Concentrations greater than 8,000 ppm isobutene were not used because of the danger of explosion. All rats survived to the

end of the study. The final mean body weights and body weight gains of all exposed groups were similar to those of the chamber controls. No exposure-related gross lesions were observed in male or female rats at necropsy. Microscopically, minimal hypertrophy of goblet cells lining the nasopharyngeal duct in the most caudal nose section was observed in some rats in each exposed group of males and in females exposed to 4,000 or 8,000 ppm.

14-WEEK STUDY IN MICE

Groups of 10 male and 10 female B6C3F$_1$ mice were exposed to isobutene at concentrations of 0, 500, 1,000, 2,000, 4,000, or 8,000 ppm 6 hours per day, 5 days per week, for 14 weeks. All mice survived to the end of the study. The final mean body weights and body weight gains of all exposed groups were similar to those of the chamber control groups. No gross or microscopic lesions were considered to be related to isobutene exposure.

2-YEAR STUDY IN RATS

Groups of 50 male and 50 female F344/N rats were exposed to isobutene at concentrations of 0, 500, 2,000, or 8,000 ppm 6 hours per day, 5 days per week, for 104 weeks.

Survival and Body Weights

Survival of exposed males and females was similar to that of the chamber controls. Mean body weights of exposed groups were generally similar to those of the chamber controls throughout the study.

2-Hydroxyisobutyric Acid Biomarker of Exposure

2-Hydroxyisobutyric acid (HIBA), the major urinary metabolite of isobutene, was measured in the urine of male and female rats as an indicator of isobutene exposure at 6, 12, and 18 months. The amount of HIBA

excreted was proportional to exposure concentration. However, when HIBA concentration was normalized to exposure concentration, the relative amount of HIBA excreted decreased with increasing exposure concentration, implying nonlinear kinetics.

Pathology Findings

The incidence of thyroid gland follicular cell carcinoma in male rats exposed to 8,000 ppm was increased compared to the chamber control group and exceeded the historical control range. The incidences of hyaline degeneration of the olfactory epithelium were marginally increased in exposed rats; however, the severities of hyaline degeneration increased with increasing exposure concentration in males and females.

2-YEAR STUDY IN MICE

Groups of 50 male and 50 female B6C3F_1 mice were exposed to isobutene at concentrations of 0, 500, 2,000, or 8,000 ppm 6 hours per day, 5 days per week, for 104 weeks.

Survival and Body Weights

Survival of exposed males and females was similar to that of the chamber controls. Mean body weights of exposed mice were generally similar to those of the chamber controls throughout the study except for female mice exposed to 2,000 or 8,000 ppm, which weighed slightly less than chamber controls from about week 52 until week 92.

2-Hydroxyisobutyric Acid Biomarker of Exposure

HIBA was measured in the urine of male and female mice as an indicator of isobutene exposure at 6, 12, and 18 months. The amount of HIBA excreted was proportional to exposure concentration. However, when HIBA concentration was normalized to exposure concentration, the relative amount of HIBA excreted decreased with increasing exposure concentration, implying nonlinear kinetics.

Pathology Findings

The incidences of hyaline degeneration of the respiratory epithelium in all groups of exposed males and females were significantly greater than in the chamber control groups. The incidences of hyaline degeneration of the olfactory epithelium in 2,000 and 8,000 ppm mice were greater than those in the chamber controls.

GENETIC TOXICOLOGY

Isobutene was not mutagenic in any of four strains of *Salmonella typhimurium*, with or without S9 metabolic activation, and no increase in the frequency of micronucleated erythrocytes was seen in peripheral blood of male or female mice treated with isobutene by inhalation for 14 weeks.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *some evidence of carcinogenic activity** of isobutene in male F344/N rats based on an increased incidence of follicular cell carcinoma of the thyroid gland. There was *no evidence of carcinogenic activity* of isobutene in female F344/N rats or male or female B6C3F$_1$ mice exposed to 500, 2,000, or 8,000 ppm.

Exposure to isobutene by inhalation for 2 years resulted in increased incidences and/or severities of nasal lesions including hyaline degeneration of the olfactory epithelium in male and female rats and mice and hyaline degeneration of the respiratory epithelium in male and female mice.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Isobutene

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Concentrations	0, 500, 2,000, or 8,000 ppm	0, 500, 2,000, or 8,000 ppm	0, 500, 2,000, or 8,000 ppm	0, 500, 2,000, or 8,000 ppm
Body weights	Exposed groups similar to chamber control group	Exposed groups similar to chamber control group	Exposed groups similar to chamber control group	2,000 and 8,000 ppm groups slightly less than chamber control group
Survival rates	7/50, 5/50, 6/50, 8/50	23/50, 19/50, 33/50, 22/50	28/50, 32/50, 27/50, 28/50	32/50, 31/50, 39/50, 33/50
Nonneoplastic effects	Nose: severity of olfactory epithelial hyaline degeneration (1.3, 1.4, 2.2, 2.6)	Nose: severity of olfactory epithelial hyaline degeneration (1.5, 2.4, 2.8, 2.8)	Nose: respiratory epithelial hyaline degeneration (6/50, 19/49, 29/50, 39/48); olfactory epithelial hyaline degeneration (6/50, 7/49, 16/50, 17/48)	Nose: respiratory epithelial hyaline degeneration (21/47, 39/50, 41/49, 48/50); olfactory epithelial hyaline degeneration (17/47, 19/50, 24/49, 27/50)
Neoplastic effects	Thyroid gland: follicular cell carcinoma (1/48, 0/48, 0/48, 5/50)	None	None	None
Level of evidence of carcinogenic activity	Some evidence	No evidence	No evidence	No evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:	Negative in strains TA97, TA98, TA100, and TA1535, with and without S9			
Micronucleated erythrocytes				
Mouse peripheral blood *in vivo*:	Negative in male and female mice			